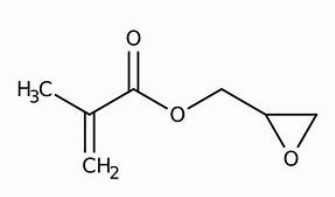
GLYCIDYL METHACRYLATE

CAS number: 106-91-2

Synonyms: Acriester G; Blemmer G; Blemmer GMA; CP-105; 2,3-Epoxypropyl methacrylate; Glycidyl alpha-methyl acrylate; Light Ester G; Methacrylic acid, 2,3-epoxypropyl ester; 2-((Methacryloxy)methyl)oxirane; Oxiran-2-ylmethyl 2-methylprop-2-enoate; 1-Propanol-2,3-epoxy methacrylate; 2-Propenoic acid, 2-methyl-, oxiranylmethyl ester; SR 379; SY-Monomer G

Molecular formula: $C_7H_{10}O_3$

Chemical structure:



TLV®–TWA, 0.01 ppm

Skin

Dermal Sensitizer (DSEN)

A2 – Suspected Human Carcinogen

TLV Recommendation

A TLV–TWA of 0.01 ppm is recommended for occupational exposure to glycidyl methacrylate to protect against upper respiratory tract irritation and damage, as well as mutagenic and probable carcinogenic effects. Glycidyl methacrylate is a highly reactive substance due to the presence of an epoxide, which likely contributes to its irritant and mutagenic properties. It is highly toxic by inhalation and highly irritating and corrosive to the skin, eyes, and respiratory tract[1] (Olson 1960 and Dupont Haskell Laboratory 1982 as cited in[2]). In a 13-day inhalation study in rabbits, olfactory epithelial degeneration, hyperplasia, erosions, ulcers, and inflammation of the nasal epithelium were observed at 10 ppm. Degeneration of the nasal olfactory epithelium was observed at 2 ppm (NOAEL=0.5 ppm) (Vedula, 1996 as cited in[2]). However, in a 13-week inhalation study in rats, 15 ppm caused very slight hyperplasia of respiratory epithelium of the nasal tissues of all animals (Landry 1996 and Ouyang-Guoshun, et al., 1990 as cited in[2]). In an inhalation developmental toxicity study in pregnant rabbits, histopathologic alterations of the nasal respiratory and olfactory epithelium (hyperplasia, necrosis, etc.) were observed in all animals at 5 ppm (maternal NOAEL=0.5 ppm). No adverse effects on any developmental parameters were reported (developmental NOAEL= 50 ppm) (Vedula 1995; 1996, as cited in[2]).

Most *in vitro* genotoxicity studies showed positive results. Several *in vivo* genotoxicity assays were also positive, but some were negative.[3] In a series of *in vivo* oral genotoxicity studies with glycidyl methacrylate, Dobrovolsky et al.[4] showed it to be positive in the rat micronucleus test for clastogenicity and aneugenicity, the Pig-a assay for mutagenicity, and the Comet assay for DNA damage (LOAEL=100 mg/kg per day). The weight-of-evidence indicates glycidyl methacrylate is a genotoxic material.

The carcinogenic potential of glycidyl methacrylate was demonstrated in 2-year inhalation studies in

B6D2F1/Crlj mice (N=50 per group) exposed to 0.6, 2.5, or 10 ppm and F344/DuCrlCrlj rats (N=50 per group) exposed to 0, 3.2, 8 and 20 ppm (JBRC 2015a, 2015b as cited in[3]). Statistically significant increases in various malignant neoplasms, compared to controls, were reported in both sexes in mice at 10 ppm and in rats at ≥3.2 ppm. Glycidol, a metabolite of glycidyl methacrylate, increased the incidence of tumors in multiple organs in rats and mice at dosages as low as 37.5 mg/kg per day and 25 mg/kg per day, respectively.[5]

Mechanistic studies have demonstrated the ability of glycidyl methacrylate to react with DNA to produce DNA adducts and genotoxic effects. There is strong evidence that glycidyl methacrylate exhibits a number of key characteristics of carcinogens: it is electrophilic, genotoxic, alters cell proliferation, causes epigenetic alterations, induces oxidative stress, and causes immortalization[3]. Glycidyl methacrylate belongs to a class of reactive glycidyl epoxides, for which one member (glycidol) has been classified as probably carcinogenic to humans (Group 2A) by IARC.

Therefore, a TLV–TWA of 0.01 ppm should protect against irritation and damage to the upper respiratory tract and should also reduce the risk of cancer resulting from alterations in DNA. Sufficient data were not available to support a TLV-STEL.

A Skin notation is recommended because the dermal LD_{50} in rabbits was 480 mg/kg[1]. Glycidyl methacrylate was shown to be a dermal sensitizer in several guinea pig assays and Dow 1992; Bibra 1988 and Ou-Yang et al. 1988 as cited in [2], which supports the assignment of a DSEN notation. The available data do not permit calculation of a TLV-SL. Experimental studies demonstrating immediate (Type-1) reactions in guinea pigs suggests the possibility of respiratory hypersensitivity (Ou-Yang et al. 1988 as cited in[2]). However, the data are insufficient to recommend an RSEN notation.

Based on positive results in *in vitro* genotoxicity assays, structural considerations and mechanistic evidence indicating the potential for carcinogenicity, equivocal *in vivo* genotoxicity tests, and the carcinogenicity of its metabolite, glycidol, the weight-of evidence indicates that glycidyl methacrylate is likely to be carcinogenic to humans.[3,6] Therefore, an A2 carcinogen classification (Probably Carcinogenic to Humans) is recommended. Because of this designation, worker exposures by all routes should be carefully controlled to levels as low as possible below the TLV.

TLV Basis

Upper respiratory tract irritation and damage, mutagenic effects, cancer

Chemical and Physical Properties[2,6-8]

Glycidyl methacrylate is a colorless liquid with an aromatic ester-like odor.

Molecular weight: 142.15

Specific gravity: 1.070

Melting point: -90°C (-130°F)

Boiling point: 189°C (372.2°F) at 760 mmHg

Vapor pressure: 0.3 mmHg at 25°C

Saturated vapor concentration: 400 ppm at 25°C

Flash point: 84°C (183°F), open cup; 76°C (168.8°F), closed cup

Flammable limits: N/A

Autoignition temperature: 389°C (732.2 °F)

Solubility: 5 to 10 mg/mL at 68°F in water. Very soluble in benzene, ethyl ether, ethyl alcohol.

Octanol/water partition coefficients: 0.96 at 25°C

Conversion factors at 25°C and 760 torr: 1 ppm = 5.81 mg/m^3; 1 mg/m^3 = 0.172 ppm

Major Sources of Occupational Exposure

Glycidyl methacrylate is used as an intermediate in the synthesis of resins, including those used in hydrogel lenses, BIS-GMA dental resin, and adhesion promotion/crosslinking comonomer (acrylic/vinyl resins)[2]. It was reported that 3,128 tons were manufactured in 2013[2]. The Food and Drug Administration (FDA) has approved homopolymers and copolymers of glycidyl methacrylate as indirect food additives for use only as a component of adhesives.

Animal Studies

Acute/Subacute

INHALATION

In rats exposed to saturated vapors of glycidyl methacrylate (about 400 ppm), the maximum survival time was 2 hours.[1] The lowest LC_{50} was 45 ppm in rats for 4 hours. It was lethal in rats, rabbits, guinea pigs, and dogs exposed to concentrations of approximately 250 to 350 ppm for 6 hours (Dupont Haskell Laboratory 1982 as cited in[2]). Corneal opacities were considered moderate at 412 ppm and slight at 269 ppm and were not reversible within 14 days post-exposure. Weight loss and labored breathing were observed at 269 and 412 ppm. A decrease in body weight was noted at 105 ppm (Nitschke et al. 1990 as cited in[2]). Changes in the lungs, thorax, and respiration were reported (Haag 1953 as cited in[2]).

In a 2-week inhalation study, rats were exposed 6 hours per day, 5 days per week, to a concentration of 35 ppm. A decrease in body weight gains, respiratory clinical signs, and higher red blood cell counts were observed compared to controls. No histopathologic changes were reported. All effects were reversible in 2 weeks (Dupont Haskell Laboratory 1982 as cited in[2]).

In a subacute inhalation toxicity study, rabbits were exposed to 0.5, 2, 5, or 10 ppm (2.9, 12, 29 or 60 m^3) 6 hours per day, for 13 consecutive days (Cieszlak et al. 1996 as cited in[2]). Degeneration of the nasal olfactory epithelium was observed at 2 ppm and olfactory epithelial degeneration, hyperplasia, erosions, ulcers and inflammation of the nasal epithelium were seen at 5 ppm and 10 ppm. The changes at 2 ppm were completely reversible after 4 weeks, but the olfactory epithelial degeneration observed at 5 and 10 ppm were only partially reversible. The NOAEL in this study was 0.5 ppm.

ORAL

The oral LD_{50} in rats ranged from 597 to 700 mg/kg (Olson 1960 as cited in[2]).[1,9] The oral LD_{50}s in mice and guinea pigs were 390 and 697 mg/kg, respectively.[9]

Rabbits given 50 mg/kg per day by gavage for 15 days exhibited serious toxicity as manifested by severe clinical signs (e.g., prostration), death, hematological changes, deterioration and bleeding in the heart, fatty changes and necrosis of the liver, hemorrhaging kidneys and brain, and ulceration of the stomach (Ou-Yang et al. 1988 as cited in[2]).

DERMAL

The dermal LD_{50} in rabbits is 480 mg/kg.[1]

SENSITIZATION

Glycidyl methacrylate produced allergic contact dermatitis in 6/6 guinea pigs in a sensitization test (details not provided Bibra as cited in[2]). It was also positive in a modified Buehler assay, with 7/10 guinea pigs responding to a dermal inductions dose of 0.4 ml of 10% or 25% glycidyl methacrylate in dipropylene glycol monomethyl ether (DPGME), 1 time per week for 3 weeks followed by a 2 week rest period, and challenged dermally with a 1% solution of glycidyl methacrylate in DPGME (Dow 1992 as cited in[2]).

In a “delayed allergy reaction test,” 10 guinea pigs were induced by dermal application or by intradermal injections with 0.1 ml of 1% glycidyl methacrylate in acetone for 10 days. The localized reactions were observed after 21 days. Hyperemia, edema, scleroma, and necrosis were observed on the treated areas, reaching a peak on the day 4, indicating the compound was in the strong allergenic category (Ou-Yang et al. 1988 as cited in[2]).

Guinea pigs injected intradermally with 0.5% glycidyl methacrylate with homologous serum albumin for 10 days and challenged at 21 days showed evidence of a Type 1, immediate hypersensitivity response with signs of breathing difficulties, wheezing, increased mouth and nose secretions, spasms, and death in the test group, but no obvious changes in the control group (Ou-Yang et al. 1988 as cited in[2]).

In another test evaluating immediate hypersensitivity reactions that resemble the passive anaphylaxis protocol, the blood of 3 animals, which were already allergic, was diluted 3, 10 and 30-fold and injected into 5 other guinea pigs. A dose-related increase in response to 0.5 ml of an intravenously administered solution of 0.1% glycidyl methacrylate homologous serum albumin solution, vs a 0.4 ml of saline solution, was observed. Localized reactions indicated a classification in the strong allergic category (Ou-Yang et al. 1988 as cited in[2]).

OTHER STUDIES

The intraperitoneal (IP) LD_{50} values in rats and mice were 290 and 350 mg/kg, respectively (Petric et al, 1973 as cited in[2]). In a dermal irritation study in rabbits, 0.1 ml of glycidyl methacrylate (92% pure) was applied for 5 days. After 1 or 2 days, redness, swelling, and blistering were observed. After 3 days there was subdermal bleeding and ulcers. Necrosis was reported after 5 days (Ou-Yang et al. 1988 as cited in[2]). In another study, a 4-hour exposure under occluded conditions resulted in moderate to severe skin irritation including necrosis with slight to moderate edema (Olson 1960 as cited in[2]). Standard DOT testing showed that 4 hours exposure induced corrosiveness, but not 1-hour exposure, indicating it should be classified as a corrosive (Packing Group 3) (Lockwood 1991 as cited in[2]).

Moderate to severe irritation and corneal damage was induced when undiluted glycidyl methacrylate was instilled directly into the eye of rabbits. Corneal damage was not reversible within 7 days post-dosing. Ocular damage was prevented by washing with water within 30 seconds[1](Olson 1960 as cited in[2]).

Subacute/Subchronic

Rats and rabbits were exposed for 6 hours per day, 6 days per week for 26 weeks to 15.3 mg/m^3 (2.6 ppm) or 206 mg/m^3 (35 ppm). The purity (92%) and vapor pressure of the glycidyl methacrylate used in these studies suggested other components (not identified) may have contributed to the toxicity observed, which were similar in both species. Adverse findings included changes in liver and spleen weight, enzyme (transaminase) levels in blood or tissue, and histopathological changes in the central nervous system (CNS), cardiovascular system, liver, and kidney. The changes were more pronounced in the high dose group and progressed after the exposures ended. The effects in the low dose group (LOAEL) were slight and generally reversible (Ouyang Guoshun et al. 1990 as cited in[2]).

In a 13-week inhalation study, rats were exposed to 0.5, 2, or 15 ppm 6 hr per day, 5 days per week. In males and females, 15 ppm caused very slight hyperplasia of respiratory epithelium of the nasal tissues of all animals. The hyperplastic respiratory epithelium was approximately 2 to 3 times as thick as that of control animals. The NOAEL and LOAEL in this study were 2 and 15 ppm, respectively (Landry 1996 as cited in[2]).

In a combined repeat-dose and reproductive and developmental toxicity screening test in rats, males were treated for 45 days and females were treated from 14 days before mating to day 3 of lactation. Doses 0, 10, 30, or 100 mg/kg per day were administered by gavage in corn oil. The key observation in this study was the squamous hyperplasia of the forestomach, which was considered to be due to irritation of this chemical. The NOAEL for effects on the forestomach was 10 mg/kg per day (MHW 1997 as cited in[2]).

A special neurotoxicity study was performed in Fischer 344 rats exposed by inhalation to glycidyl methacrylate at approximately 0.5, 2, or 15 ppm (2.9, 12, 87 mg/m^3), 6 hours per day, 5 days per week for 13 weeks. A functional observation battery (FOB) and motor activity (MA) were conducted preexposure and at the end of each month of exposure, along with a wide range of specialized neurological tests and a comprehensive neuropathological examination. At week 4, there was a low incidence of nasal discharge and enlarged nostrils at 0.5 and 2 ppm. There were no treatment-related effects in any of the other measures, and there was no evidence of neurotoxic effects at any exposure level. The LOAEL was 0.5 ppm for upper respiratory effects in this study (Mattsson et al. 1996 as cited in[2]).

Chronic/Carcinogenicity

In a 1-year study in rats, doses of 0.1 and 0.3 mg/kg per day, given days per week by gavage did not produce any discernable adverse effects. However, the doses were low and the study was poorly reported (Hadidian et al. 1968 as cited in[2]).

The carcinogenic potential of glycidyl methacrylate was demonstrated in 2-year inhalation studies in B6D2F1/Crlj mice (N=50/group) exposed to 0.6, 2.5, or 10 ppm and F344/DuCrlCrlj rats (N=50 per group) exposed to 0, 3.2, 8, and 20 ppm. Statistically significant increases in proliferative lesions were observed at 10 ppm in mice and ≧3.2 ppm in rats, and there were positive trends observed for several tumor types (JBRC 2015a, 2015b).

Non-neoplastic lesions mice, including transitional cell hyperplasia of the nasal cavity (males and females) and angiectasis of the nasal cavity (females) were observed at 10 ppm. In rats, non-neoplastic lesions in the nasal cavity including squamous cell hyperplasia with atypia (males and females) were observed at 20 ppm, squamous cell metaplasia in the respiratory epithelium was seen in females at concentrations > 3.2 ppm and in males at 8 and 20 ppm, and transitional epithelium hyperplasia (males and/or females) was reported at ≥ 3.2 ppm (JBRC 2015a, 2015b as cited in[3]).

Malignant neoplasms were also increased compared to controls in both sexes in mice and rats. In both male and female mice, increased nasal cavity hemangiomas and hemangiosarcomas (0/50, 0/50, 4/50, 16/50 combined tumors at 0, 0.6, 2.5 and 10 ppm, respectively for males; 0/50, 0/50, 4/50, 11/50 combined tumors in females) and harderian gland tumors (1/50, 1/50, 5/50, 5/50 in males and 1/50, 1/50, 2/50, 4/50 in females) were observed. In female mice, bronchioalveolar carcinomas and uterine histiocytic sarcomas were also observed (JBRC 2015b as cited in[3]). In mice, tumors were significantly increased ($p < 0.05$ or 0.01) only at the highest concentration (10 ppm), but there was also a significant dose-related trend below this level.

In male and female rats, increased nasal squamous cell sarcomas were reported. Rare nasal cavity neuroepithelial carcinoma (0 of 50, 0 of 50, 0 of 50, 29 of 50 in males and 0 of 50, 0 of 50, 0 of 50,10 of 50 in females at 0, 3.2, 8, and 20 ppm). Peritoneal mesotheliomas (1 of 50, 7 of 50, 16 of 50, 14 of 50) were seen in male rats, and uterine endometrial stromal sarcomas (1 of 50, 1 of 50, 1 of 50, 5 out of 50) were seen in female rats (JBRC 2015a as cited in[3]). In rats, most tumors were significantly increased ($p < 0.01$) only at the highest concentration. The exception was with peritoneal mesotheliomas, which were significantly increased ($p < 0.05$) at 3.2 ppm and 8 and 20 ppm ($p < 0.01$).

Glycidyl methacrylate was classified by IARC[3] as probably carcinogenic to humans (Group 2A) on the basis of sufficient evidence of carcinogenicity in experimental animals and strong mechanistic evidence. There is strong evidence that glycidyl methacrylate exhibits key characteristics of carcinogens. It belongs to a class of reactive glycidyl epoxides, for which one member (glycidol) has been classified as probably carcinogenic to humans.[3]

Glycidol is also a metabolite of glycidyl methacrylate and, when used as a test material of 94% purity, increased the incidence of tumors in multiple organs in rats and mice at dosages as low as 37.5 mg/kg per day and 25 mg/kg per day, respectively.[5] There was a statistically significant increase in the incidence of numerous tumors of the mammary gland (females and males), forestomach, mouth or tongue, clitoral gland, Zymbal gland, thyroid gland, skin, intestine, and hematopoietic system (leukemia). In B6C3F1 mice, there was also an increased in the incidence of multiple tumors, including Harderian gland, liver, forestomach, skin, lung, mammary gland and uterus. According to the National Toxicology Program Review Panel, there was clear evidence of carcinogenicity in male and female Fischer 344 rats and B6C3F1 mice.[3,5]

Genotoxicity

In Vitro Studies

The mutagenicity of glycidyl methacrylate was evaluated in Salmonella tester strains TA98, TA100, TA1535 and TA1537 (Ames Test), both in the presence and absence of added metabolic activation by Aroclor-induced rat liver S9 fraction. There was a positive response at all concentrations tested in tester strains TA100 and TA1535 without activation, and in tester strain TA1535 with activation. Positive

responses were also observed in tester strain TA100 at 100-1000 ug/plate in the presence of activation, but not at 32 ug/plate (Goodyear 1981 as cited in[2]).

Glycidyl methacrylate induced a significant, reproducible, dose-dependent increase in the number of revertant colonies per plate for tester strain TA 100 and TA 1535 with and without metabolic activation. Bacterial gene mutation is positive with and without metabolic activation. Glycidyl methacrylate showed a positive result in TA97, TA100, and TA1535, with and without metabolic activation, but not in TA98.[10]

It was also positive in the bacterial gene mutation assay using *Salmonella typhimurium* TA95, TA100 at concentrations 112, 224, 448, 896 ug/plate with and without metabolic activation (Ou-Yang et al. 1988 as cited in[2]).

Positive results were also reported in the SOS-Chromotest using *Escherichia coli* PQ 37 at concentrations of 0.1, 0.3, and 1.0 mmol/L, with and without metabolic activation.[11]

Glycidyl methacrylate was positive in the *in vitro* chromosomal aberration assay in CHL/IU cells, with and without metabolic activation (Ministry of Health and Welfare: Japan 1997 as cited in[2]).

A Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl transferase (CHO/HGPRT) forward gene mutation assay in Chinese hamster ovary cells was positive with metabolic activation at 25-600 ug/ml and negative without metabolic activation at 5-80 ug/ml (Linscombe and Engle 1995 as cited in[2]).

A sister chromatid exchange (SCE) assay in Chinese hamster V79 cells was positive without metabolic activations at concentrations of 0, 0.02, 0.039, 0.078, 0.16, 0.31 mM.[12]

Unscheduled DNA synthesis assays in human lymphocytes and rat lymphocytes were also positive.[13] Glycidyl methacrylate was also shown to induce non-reverse type inhibition of the DNA replication in rat and human lymphocytes (Xie et al. 1989 as cited in[2]).

Positive results were reported in a Transformation assay in Golden Syrian hamster embryo cells (diploid) at concentrations of 0.9 to 14.2 mg/L (Yang et al. 1996 as cited in[3]), A Transformation assay in Syrian hamster embryonic cells was also positive (Xie et al. 1992 as cited in[2]).

The binding between glycidyl methacrylate and DNA *in vitro* to plasmid pBR322 was verified spectrophotometrically. This provides evidence that glycidyl methacrylate, when covalently linked to the plasmid DNA, can give rise to a premutagenic lesion of DNA that could be converted into a point mutation [14]. In a DNA binding study, the absorption spectrum shift method was used to show that the bond between DNA and GMA was covalent and that the binding force was strong.[13]

In Vivo Studies

Several *in vivo* genotoxicity assays were also positive, but others were equivocal or negative. A mouse micronucleus assay using the Crj: BDF1 strain was positive when single oral dosages were given by gavage at dosages of 188, 375, and 750 mg/kg for males and 250, 500, and 1,000 mg/kg for females (Ministry of Health and Welfare: Japan 1997 as cited in[2]). A significant increase in the frequency of micronucleated polychromatic erythrocyte in both sexes, compared to controls, was seen at the highest doses and there was a significant trend observed at lower dosages.

A micronucleus test conducted in male mice given glycidyl methacrylate by intraperitoneal administration up to 300 mg/kg was considered equivocal due to an increase in the number of cells with micronuclei, but this change was very slight and had an inverse dose-response (Ou-Yang et al. 1988 as cited in[2]).

In another micronucleus test in mice by intraperitoneal administration, negative results were reported at dosages up to 300 mg/kg (Lick et al. 1995 as cited in[2]). Likewise, a mouse micronucleus assay using intraperitoneal (IP) doses up to 464 mg/kg was also negative (INBIFO 1979 as cited in[2]). In an oral micronucleus test in mice, the frequency of micronucleated polychromatic erythrocytes was significantly increased in both sexes at the highest doses (750 mg/kg for male and 1,000 mg/kg for female), compared to control.[15] Glycidol, a metabolite of glycidyl methacrylate, was positive in the mouse micronucleus test at an IP doses of 150 mg/kg.[5]

In an *in vivo* unscheduled DNA synthesis (UDS) test in male mice (route and doses unknown), unscheduled DNA synthesis was increased in the germ cells, but this change was very slight and not dose-related. The results were considered equivocal.[13]

There was no increase in the induction of gene mutations at the lacI locus in the respiratory epithelium of transgenic Big Blue® Fischer 344 rats (15 rats per group) exposed to concentrations of 1, 10, and 25 ppm (5.82, 58.2, and 145.5 mg/m^3), 6 hours per day, 5 days per week, for 4 weeks. Calculated daily dose were 0.71, 7.08, 17.70 mg/kg per day, respectively. Histopathological lesions were observed in the nasal epithelium at 25 ppm, indicating this was a maximum tolerated dose (Gollapudi et al., 1999 as cited in[2]).

Dobrovolsky et al.[4] performed a novel series of *in vivo* genotoxicity studies with glycidyl methacrylate showing it was a systemic *in vivo* genotoxicant. It was positive in the rat micronucleus test for clastogenicity and aneugenicity, the Pig-a assay for mutagenicity, and the Comet assay for DNA damage.

Reproductive/Developmental Toxicity

In a developmental toxicity study in Wistar rats, pregnant females were exposed to 5.38, 10.76, 21.52, or 108.0 mg/kg per day on gestation days 5 to 15. At the highest dose, a non-dose-related increase in fetal resorptions was observed in the presence of maternal toxicity (significant decrease in body weight gain). No teratogenic effects were observed. The NOAEL for fetal and maternal toxicity was reported to be 21.52 mg/kg per day (Ou-Yang et al. 1988 as cited in[2]).

Pregnant rabbits were exposed to 0, 5, 10, or 50 ppm (0, 29.1 58.2, or 291 mg/m^3), 6 hours per day, on days 7 through 19 of gestation. The highest dose group needed to be euthanized due to severe maternal toxicity (Vedula 1995 as cited in[2]). Histopathologic alterations of the nasal respiratory and olfactory epithelium (hyperplasia, necrosis, etc.) were observed in all animals at the lower concentrations (maternal LOAEL=5 ppm). No adverse effects on any developmental parameters were reported (developmental NOAEL $\geq$ 10 ppm). In a follow-up study pregnant rabbits were exposed to 0, 0.5, 2, or 10 ppm 6 hours per day, on days 7 through19 of gestation. Maternal toxicity was manifested as inflammation of the nasal olfactory and respiratory epithelium at 2 and 10 ppm (maternal NOAEL=0.5 ppm). There were no teratogenic effects reported (Vedula 1996 as cited in[2]).

In a Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test in Cij: CD (SD) rats, oral (gavage) doses of 10, 30, 100 mg/kg per day (in corn oil) were administered for 40 to 47 days. Fertility was significantly decreased at 100 mg/kg. No change in the number of gonocytes per Sertoli cell was observed in epithelium of seminiferous tubules (stage VIII) of all survival males at 100 mg/kg. There were no statistically significant changes in male or female reproductive parameters or histopathology of the testes at 10 or 30 mg/kg per day. The parental NOAEL was 30 mg/kg per day and the F1 offspring NOAEL was 100 mg/kg per day (Ministry of Health and Welfare: Japan 1997 as cited in[2]).

In a test to evaluate potential effects on spermatogenesis, male mice were given intraperitoneally doses of 0, 5, 25, or 100 mg/kg per day for 5 days. Decreased caudal epididymal weights and slightly lower testicular weights were observed at 100 mg/kg. Decreased sperm counts and increased abnormal sperm were observed at 25 and 100 mg/kg per day. The NOAEL for effects on spermatogenesis was 5 mg/kg per day (Vedula et al., 1994 as cited in[2]).

Absorption, Distribution, Metabolism, and Excretion

The toxicokinetics of glycidyl methacrylate was investigated in rabbits given an intravenous injection of 200 mg/kg. Over 95% of the compound was eliminated from the blood in 10 minutes. *In vitro* metabolism studies showed the highest rates of metabolism in the blood and liver. Using competitive inhibition studies with tri-o-cresyl phosphate, it was demonstrated that glycidyl methacrylate is metabolized by carboxylesterase (Tao et al.1988 as cited in[2]).

The metabolism of glycidyl methacrylate likely proceeds by at least 2 different and competing enzyme systems, epoxide hydratase and non-specific carboxylesterases. In rabbits, the carboxylesterase route of metabolism predominates in the nasal tissue, yielding glycidol, which is carcinogenic, and methacrylic acid, which is quite irritating. In rats and humans, the epoxide hydratase route would likely predominate, first producing glycerol methacrylate, which is converted to glycerol and methacrylic acid by

carboxylesterase[16-19](Pacifici et al. 1981 as cited in[2]).

Overall, the conclusion is that glycidyl methacrylate is extensively metabolized into glycidol (and methacrylic acid) and is expected to produce similar systemic effects as glycidol.[20]

Human Studies

Symptoms of exposure may include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, dizziness, tiredness, nausea, vomiting, chest pain, muscle pain, flushing, and tingling of hands and feet. Allergic reactions may include rash, itching, and swelling.[6,8]

Three cases of allergic contact hypersensitivity to glycidyl methacrylate were reported in workers manufacturing sealant adhesive. When tested as a 1% using open and closed patch testing, symptoms included significant erythema, edema, and vesiculation indictive of a strong sensitization response.[21]

A 31-year-old non-atopic woman, who had worked as a chemist and mixed emulsions used to impregnate paper and textile materials to make them oil- and water-resistant, had a history of recurrent acute vesiculopapular hand dermatitis with severe itching and burning. She had been in contact with acrylate derivatives (glycidyl methacrylate, ethoxyethyl acrylate, and others) and when patch tested, reacted to nickel (consistent with her allergy to jewelry), glycidyl methacrylate (0.01% and 0.05%) and ethoxyethyl acrylate.[22]

TLV Chronology

Date	Action	Determinant	TLV
2022	Adopted	TLV-TWA Skin DSEN A2, Suspected Human Carcinogen	0.01 ppm

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